REMARKS

Status of the claims:

With the above amendments, claims 1-3 and 8 have been amended and claims 9 and 10 have been added. No new matter has been added by way of the above amendment. The amendment to claim 1 has support at page 6, lines 21-22. The amendments to claims 2, 3 and 8 are simply for form. Claim 9 has support in original claim 8. claim 10 has support in original claim 3. Accordingly, claims 1-10 are pending and ready for further action on the merits. Reconsideration is respectfully requested in light of the following remarks.

Abstract

The Examiner asserts that the instant application lacks an abstract. Attached to this reply, please find an Abstract. Withdrawal of the objection is warranted and respectfully requested.

Rej ctions under 35 USC §112, second paragraph

Claims 1-8 are rejected under 35 USC §112, second paragraph as being indefinite.

The Examiner asserts that in claim 1 "comprising" has been misspelled as "compromizing". Claim 1 has been amended to correct

this error. Withdrawal of the rejection is warranted and respectfully requested.

The Examiner asserts that claim 1 is indefinite for the use of the term "DMSO". Applicants have amended claim 1 to recite "dimethyl sulfoxide". Applicants believe that with this amendment that the rejection has been obviated. Withdrawal of the rejection is respectfully requested.

The Examiner has rejected claim 8 for the use of the term "such as". Applicants have amended claim 8 so that it no longer contains this term. Withdrawal of the rejection is warranted and respectfully requested.

Rejections under 35 USC §102

Claims 1-2 are rejected under 3 USC §102(b) as being anticipated by Lebel et al. (Int. Arch. Allergy Immunol., Vol. 116, pp. 284-287, (1998)).

Claims 1-2 are rejected under 3 USC §102(b) as being anticipated by Kessler et al. (Biochemical Pharmacology, Vol. 40, pp. 169-173, (1990)).

These rejections are traversed for the following reasons.

Neither Lebel et al. nor Kessler et al. can anticipate the instant invention because they simply fail to disclose the elements in the instantly claimed invention.

First, neither Lebel et al. nor Kessler et al. disclose a phamaceutical composition. For this reason alone, the rejection is inapposite.

As a point of illustration, Applicants point out that Lebel et al. disclose an *in vitro* study on dissociated nasal polyp cells in a test tube. Lebel et al. do not disclose or suggest an *in vivo* study on a whole organism, and nowhere do the authors suggest that their *in vitro* cyclosporin solution be adapted for use in animals or humans for any purpose. Thus, Lebel et al. have not produced a pharmaceutical composition that anticipates claims 1 and 2. In other words, while the Lebel et al. authors discuss the many known effects of cyclosporin on p. 286, they nowhere suggest that a cyclosporin-DMSO pharmaceutical drug be used in humans or animals.

Second, instant claim 1 has been amended to recite a particular minimal concentration of cyclosporin in the pharmaceutical composition. This element is not met by Lebel et al. The maximal concentration of cyclosporin Lebel et al. use in their *in vitro* study is 10 microMolar. With a molecular weight of 1202.6, one molar would be 1202.6 grams cyclosporin per liter, one milliMolar would be 1.2 grams cyclosporin per liter solution and one microMolar would be 0.0012 grams of cyclosporin per liter. Thus, Lebel et al. maximal cyclosporin concentration of 10 micromolar would give only 0.012 grams (or 12 mg) cyclosporin per

liter. Given that a standard human daily dose of cyclosporin for immunosuppression is 5 mg/kg, or for a 70 kg person, a quantity of 350 mg per day of cyclosporin would be needed. At the Lebel et al. maximum cyclosporin concentration, one would have to administer a fluid volume of over 29 liters a day to a person. The liquid weight of 29 liters would be over 52 lbs per day, which is not generally considered a practical or safe pharmaceutical composition, or even a possible volume of water to be administered to a person or patient. Thus, even the maximal concentration described by Lebel et al. in their *in vitro* study cannot be considered as having disclosed a pharmaceutical composition.

Moreover, the composition amount in cyclosporin disclosed by Lebel et al. falls outside of the scope of the instantly claimed invention. In the instant invention, the lowest amount (0.1% by weight of the total composition) would be 120 mg cyclosporin per liter, 10 times greater than that described by Lebel et al. While a patient would need to receive 2.9 liters of fluid per day, this would be at least physiologically possible. Thus, claims 1 and 2 are not anticipated by Lebel et al.

For the above reasons, Applicants submit that the anticipation rejection over Lebel et al. is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

With regards to the rejection over Kessler et al., Applicants traverse.

The Kessler article is pure chemical basic research on the chemical conformational structures of cyclosporin when it is dissolved in a variety of mostly toxic organic solvents for the purpose of better understanding the charge and molecular interactions of cyclosporin using the physical laboratory tool of nuclear magnetic resonance (NMR) spectroscopy. Kessler et al. do not disclose pharmaceutical compositions that can be administered to animals.

Kessler et al. describe a number of organic solvents including THF, or toxic tetrahydrofuran, deuterated chloroform, highly toxic carbon tetrachloride, and lithium salts, as well as water and DMSO. Based on the high toxicity of most of the solvents used in this theoretical article on the structure of cyclosporin in different chemical environments, the average practitioner of the art would be hesitant to try any of them in creating a pharmaceutical for use in a living animal. In other words, the Kessler et al. paper does not disclose "a pharmaceutical composition".

The highly theoretical and medically obscure Kessler article can hardly be considered to disclose, suggest or induce the use of DMSO and cyclosporin together in a pharmaceutical composition.

Below, are the only 2 mentions of DMSO in the article, which clearly are unrelated to even living cells in an in vitro experiment, much less a pharmaceutical composition for use in animals or humans.

Kessler et al. at page 172 column 1 state:

> *The calculations started from the X-ray structure and conformational changes such as cis-trans isomerism about peptide bonds cannot occur in the time scale of the calculations. However, those inter-conversions are observed already in DMO and are expected to occur also in water.*

Kessler et al. at page 172 column 2 state:

> *Whereas there was no distinct difference between the structure of CSA in CDCL3 and THF, the addition of LiCl caused a conformational change. Also, using polar solvents (DMSO, water) induced conformational changes in the backbone as well as the side chains.*

From these passages it would be apparent to one of ordinary skill in the art that Kessler et al. do not disclose a "pharmaceutical composition" as disclosed and claimed in claim 1 of the instant invention.

Moreover, the cyclosporin dissolved in DMSO is highly unlikely to be in a physiological buffer for nuclear magnetic resonance spectroscopy experiments since the addition of any salts would need to be quantified because of their effect altering the spectra sought. For example in Kessler et al., the salt lithium chloride has a marked effect on the conformation of cyclosporin.

For the above reasons, Kessler et al. do not disclose all of the elements of the instantly claimed invention. The Kessler et al. article does not anticipate claims 1 and 2. Withdrawal of the rejection is warranted and respectfully requested.

R jections under 35 USC §103

Claims 3-8 are rejected under 35 USC §103(a) as being unpatentable over Lebel et al. taken with Falk '834 (US Patent No. 5,827,834).

This rejection is traversed for the following reasons.

Present Invention

The present invention, as recited in claim 1 relates to a pharmaceutical composition of matter in the form of a solution concentrate comprising a cyclosporin dissolved in dimethyl sulfoxide (DMSO) wherein the concentration of cyclosporin is at least 0.1% by weight of the total composition.

Disclosure of Lebel et al.

Lebel et al. disclose an *in vitro* study on dissociated nasal polyp cells in a test tube. Lebel et al. discuss the many known effects of cyclosporin on page 286 of the article.

Lebel et al. do not disclose or suggest an *in vivo* study on a whole organism, and nowhere do the authors suggest that their *in vitro* cyclosporin solution be adapted for use in animals or humans for any purpose. Moreover, Lebel et al. nowhere suggest that a cyclosporin-DMSO pharmaceutical drug be used in humans or animals.

Disclosure of Falk '834

Falk '834 discloses a method of treating anorectal disease which comprises applying to anorectal tissue in need of such treatment an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount of up to about 10% by weight.

Removal of the Rejection over Lebel et al. taken with Falk '834

Falk '834 relates to the art of the current patent application in only the most obscure ways. The essence of Falk '834 is that hyaluronic acid makes other drugs more effective, or reduces the other drugs side effects. Hyaluronic acid is seen to enhance a second drug's penetration of scar tissue and other tissues improving the efficacy of that second drug. (see column 10 lines 25-30 in Falk '834). One drug (amongst a host of drugs) that hyaluronic acid is reported to enhance the penetration into tissues

is cyclosporin (column 10, line 23, column 11 lines 7 and 45, column 12, lines 13 and 51, column 13, lines 17 and 49, and column 19, line 55). Of interest, none of the 40 (Cases I-XL) patients were treated with cyclosporin and hyaluronic acid suggesting that even this association is tenuous. The last paragraph of Falk '834 describes a rat skin grafting experiment where hyaluronic acid enhanced the survival of grafts treated with cyclosporin.

It is respectfully submitted that the Examiner has inverted the meaning of Falk '834 when the Examiner states that DMSO helps hyaluronic acid enter the brain in brain tumor patients. The meaning of Falk '834 is the opposite, that hyaluronic acid facilitates the entry of DMSO into the brain where the DMSO then has an enhanced therapeutic effect. Please see column 17 lines 8-13 wherein Falk '834 says

> *In patients suffering from brain tumors, the swelling must be reduced. Administration of dimethyl sulfoxide (DMSO) in amounts of less that 100 gm daily in a 10% solution in hyaluronic acid (sodium hyaluronate) 300-500 mg reduces acute brain and spinal edema.*

From this paragraph it should be apparent to those of ordinary skill in the art that hyaluronic acid is used to facilitate the transfer of DMSO to reduce acute brain and spinal edema. Thus, DMSO is thought to be the active ingredient in Falk '834.

Moreover, Falk '834 is only tangentially applicable to the instantly claimed invention. While Falk '834 discloses both DMSO

and cyclosporin, it is NEVER in combination together, and always in relation to co-administration with hyaluronic acid. In the one rat immunosuppression example where cyclosporin is actually used in any experimental situation, the cyclosporin is given with hyaluronic acid and not with DMSO. Thus, applicant respectfully submits that someone skilled in the art could not be expected to arrive at the present invention for an *in vivo* pharmaceutical formula for administration to humans by combining the Lebel et al. *in vitro* study using unpharmacologic minute doses of cyclosporin with a vanishing small quantity of DMSO on dissociated nasal polyp cells in a test tube, together with the Falk '834 where hyaluronic acid is used separately to enhance the penetration of either DMSO or cyclosporin into tissues, but never mentions the combination of DMSO and cyclosporin TOGETHER with or without hyaluronic acid.

For the above reasons, Applicants submit that the Examiner has failed to make out a *prima facie* case of obviousness regarding the rejection over Lebel et al. taken with Falk '834. Three elements are required to make out a prima facie case of obviousness.

1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

2) There must be a reasonable expectation of success.

3) The prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. See MPEP §2143 and *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants submit that none of these elements are met. Neither of Lebel et al. nor Falk '834 disclose or suggest a pharmaceutical composition containing both DMSO and cyclosporin. Lebel et al. fails to disclose a pharmaceutical composition as argued above and Falk '834 fails to disclose DMSO and cyclosporin together. Accordingly, because to two references fail to disclose all of the elements of the instant invention one of ordinary skill in the art would not expect success. Finally, the requisite motivation for combining the references also appears to be lacking.

For all these reasons, Applicants submit that the 35 USC §103(a) rejection over Lebel et al. taken with Falk '834 is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

With the above remarks and amendments, it is believed that the claims, as they now stand, define patentable subject matter such that a passage of the instant invention to allowance is warranted.

A Notice to that effect is earnestly solicited.

If any questions remain regarding the above matters, please contact Applicant's representative, T. Benjamin Schroeder (Reg. No. 50,990), in the Washington metropolitan area at the phone number listed below.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition a one (1) month extension of time for filing a response in connection with the present application. The required fee of $55.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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Attachment(s): Abstract of the Disclosure